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Introduction

Prior research indicates pain sensitivity varies across the menstrual cycle, with the luteal phase generally associated with enhanced pain and noci-reactivity. Although the mechanisms underlying the relationship between menstrual phase and pain have yet to be established, cyclical variation in sex hormones may account for changes in pain modulation. However, prior research in this area has suffered from methodological limitations such as small sample size, lack of verification of ovulation, failure to assess multiple pain outcomes, low-powered statistical methodologies, and inadequate assessment of menstrual cycle regularity. Because of these limitations, ascertaining the relationship between the menstrual cycle and pain processing is challenging. The current study was designed to address some of these limitations by (i) assessing several pain outcomes from multiple stimulus modalities, (ii) recruiting a relatively large sample size, (iii) verifying menstrual phase timing by luteinizing hormone tests and daily menstrual calendars, (iv) having women monitor their menstrual phases over three menstrual cycles to verify cycle regularity, and (v) using powerful mixed model statistical analyses.

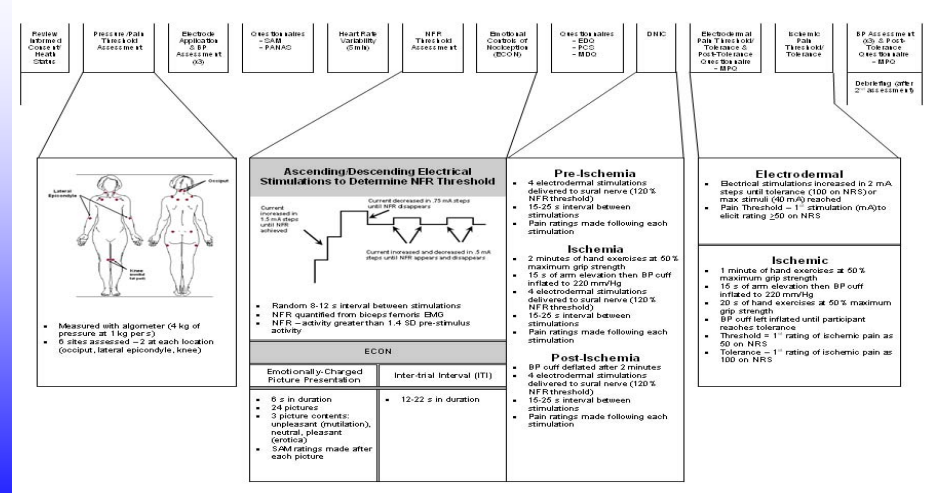
Objective

- To determine if menstrual cycle phase-related changes exist in experimental pain sensitivity including electrocutaneous pain threshold/tolerance, physiological pain responses (i.e., NFR), ischemia pain threshold/tolerance, subjective sensory and affective pain, and pressure-pain

Participants

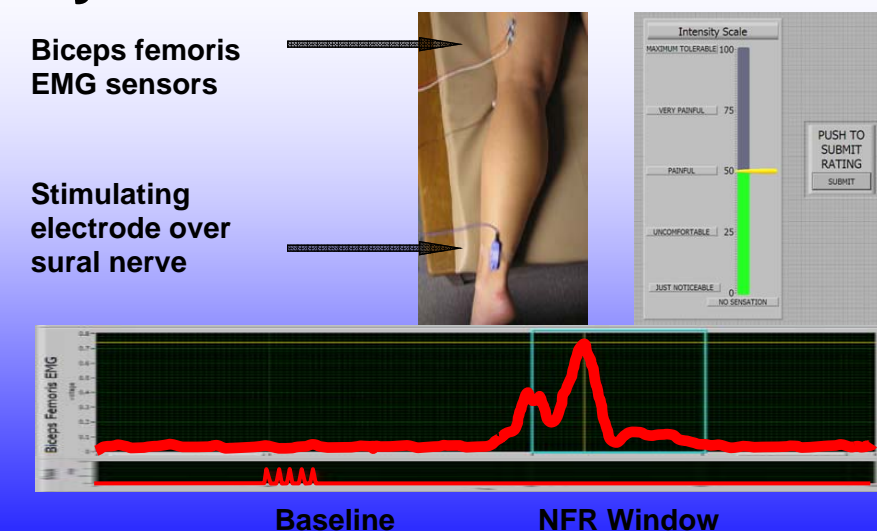
- Healthy Female Participants: N = 41**
 - Participant Characteristics: White, non-Hispanic (71%); married (73%); employed full-time (56%); yrs of education = 15 (SD = 1.79); average age = 31.00 yrs (SD = 8.86); average menstrual cycle length = 29 (SD = 3.28); average length of luteal phase = 15 days (SD = 3.48)
- Exclusion Criteria:**
 - <18 years of age
 - Failure to regularly cycle within 2 months of study inclusion
 - Use of hormone preparations within past 6 months
 - Pregnant within past 6 months
 - Menopausal or post-menopausal
 - Current acute illness
 - Cardiovascular, neurological, circulatory and/or hearing problems
 - Chronic pain condition (e.g., back pain)
 - Recent use of analgesic medication
 - Current use of anxiolytic and/or antihypertensive medication
 - Recent psychological trauma

Experimental Procedure



Pain Sensitivity: Electrocutaneous

- Nociception Flexion Reflex (NFR) Threshold:** biceps femoris EMG activity in the 90-150 ms post-stimulus window.
 - NFR is a spinally-mediated protective withdrawal reflex elicited by Aδ fiber activation
 - NFR threshold correlates highly with pain threshold
- Pain Threshold:** Ascending series of 2 mA stimulations presented; threshold = first stimulus (in mA) rated ≥ 50 on numerical rating scale.
- Pain Tolerance:** Ascending series continued until pain rating of 100 achieved or max intensity (40 mA) reached.



Pain Sensitivity: Ischemic

- Procedure:** 1 min. of hand exercises at 50% maximum grip strength, 15 sec. of arm elevation for exsanguination, blood pressure cuff inflated to 220 mg/Hg, 20 sec. of hand exercises at 50% maximum grip strength, blood pressure cuff left inflated until participant reached tolerance
- Ischemic Pain Threshold:** 1st rating of ischemic pain as ≥ 50 on numerical rating scale
- Ischemic Pain Tolerance:** 1st rating of ischemic pain as 100 on numerical rating scale



Pain Sensitivity: MPQ Ratings

- McGill Pain Questionnaire (MPQ):** Self-report measure used to rate experience of pain during sensitivity testing.
 - MPQ Sensory—reflects sensory aspect of pain experience (e.g., throbbing, burning)
 - MPQ Affective—reflects affective aspect of pain experience (e.g., tiring, fearful)
- Questionnaire administered following electrocutaneous pain threshold/tolerance procedure and ischemia pain threshold/tolerance procedure

Pain Sensitivity: Mechanical Pressure-Pain

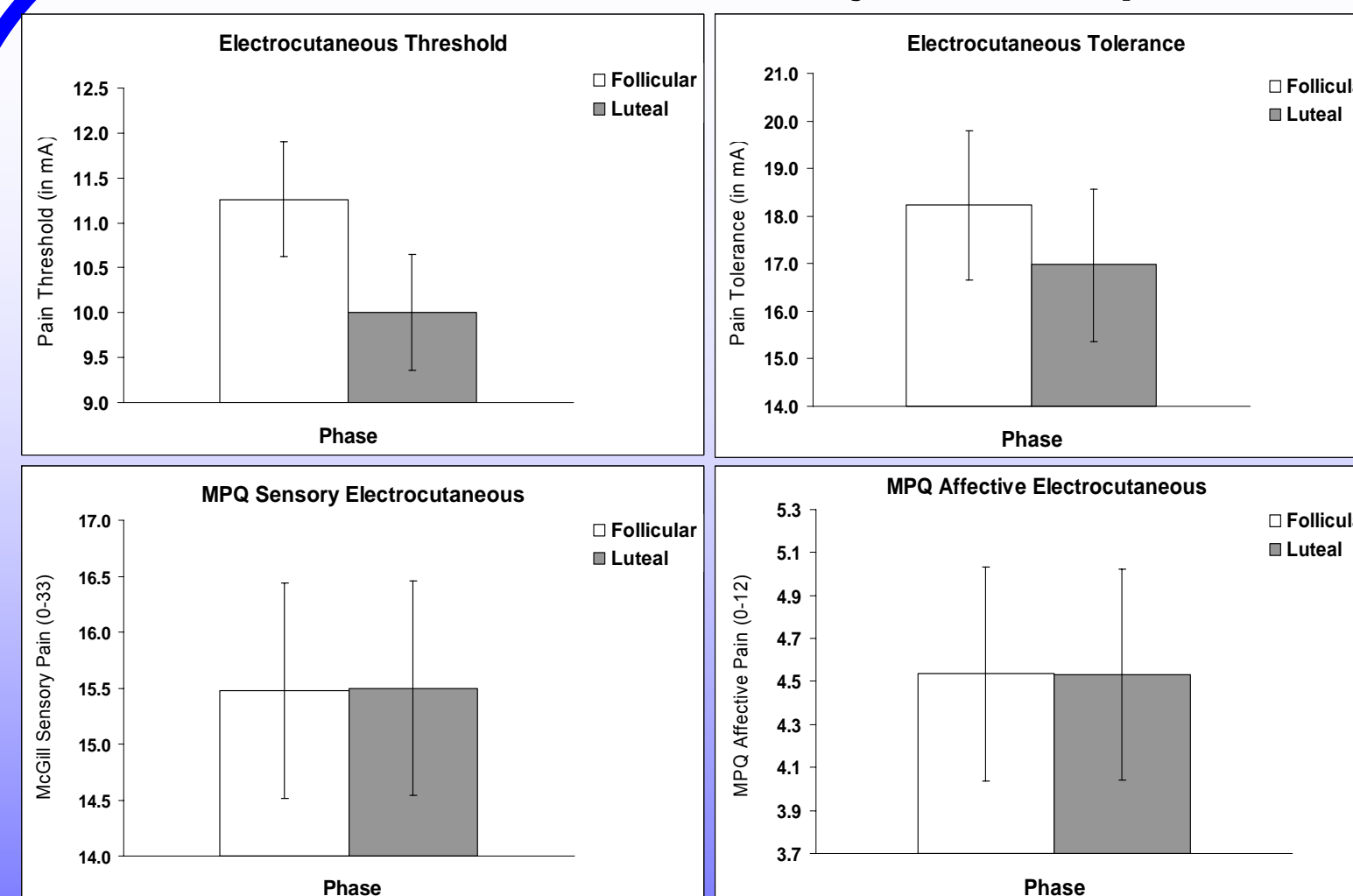
- Measured with pressure algometer (1 kg of pressure exerted per sec. until participant indicated it as being painful (pain threshold))
- 6 sites assessed—2 at each location (occiput, lateral epicondyle, fatty knee pad)



Data Analysis

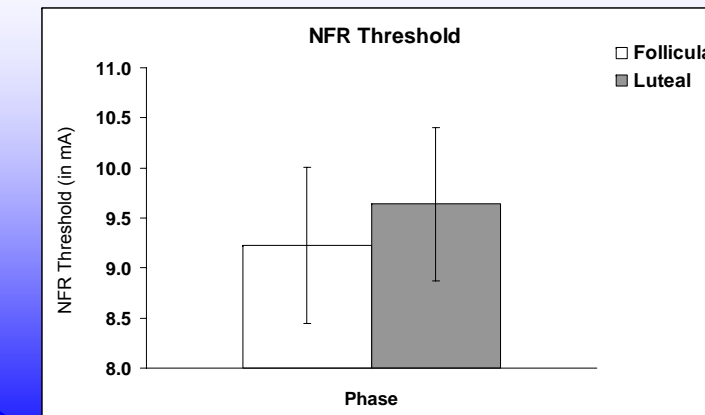
- MIXED procedure in SPSS 14.02 used
- Menstrual Phase was entered as a nominal variable
- Follow-up mean comparisons to significant F-tests were conducted with Fisher's LSD tests
- Testing order (follicular-luteal vs. luteal-follicular) was entered as an IV in all analyses

Results: Electrocutaneous Subjective Responses



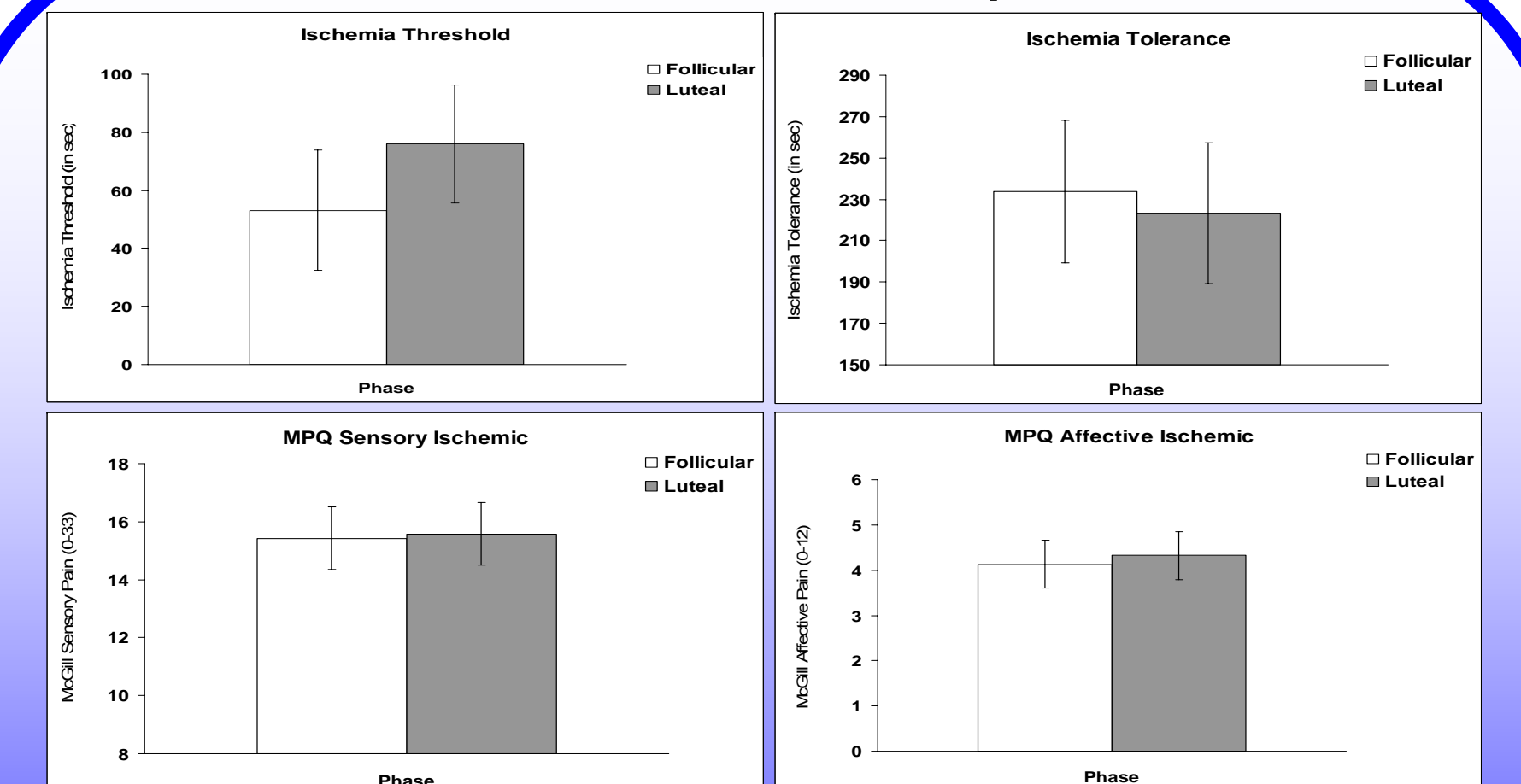
- Electrocutaneous Threshold:** The main effect of Menstrual Phase ($F[1, 36] = 4.33, p < .05$) was significant for Electrocutaneous Threshold.
- Electrocutaneous Tolerance:** The main effect of Menstrual Phase ($F[1, 34] = 2.91, p = .10$) was not significant for Electrocutaneous Tolerance.
- MPQ Sensory:** The main effect of Menstrual Phase ($F[1, 35] = .00, p = .97$) was not significant for MPQ Sensory Electrocutaneous Ratings.
- MPQ Affective:** The main effect of Menstrual Phase ($F[1, 35] = .00, p = .99$) was not significant for MPQ Affective Ischemic Ratings.
 - Results indicate electrocutaneous pain sensitivity does not differ greatly across the menstrual cycle; however, thresholds were significantly lower during the late-luteal phase of the menstrual cycle.

Results: Electrocutaneous Physiological Responses (NFR)



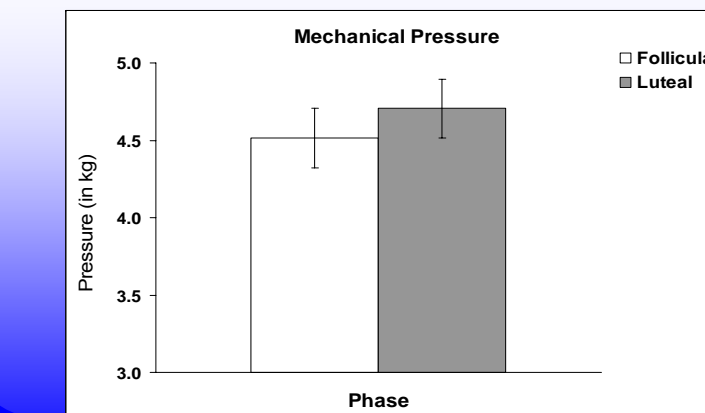
- NFR Threshold:** The main effect of Menstrual Phase ($F[1, 30] = .29, p = .69$) was not significant for NFR Threshold.
- This indicates NFR Threshold did not differ across the mid-follicular and late-luteal phases of the menstrual cycle.

Results: Ischemic Pain Responses



- Ischemia Threshold:** The main effect of Menstrual Phase ($F[1, 39] = .88, p = .35$) was not significant for Ischemia Threshold.
- Ischemia Tolerance:** The main effect of Menstrual Phase ($F[1, 37] = .13, p = .73$) was not significant for Ischemia Tolerance.
- MPQ Sensory:** The main effect of Menstrual Phase ($F[1, 34] = .06, p = .81$) was not significant for MPQ Sensory Ischemic Ratings.
- MPQ Affective:** The main effect of Menstrual Phase ($F[1, 37] = .19, p = .67$) was not significant for MPQ Affective Ischemic Ratings.
 - Results indicate ischemic pain sensitivity does not vary across the mid-follicular and late-luteal phases of the menstrual cycle.

Results: Mechanical Pressure-Pain



- Mechanical Pressure:** The main effect of Menstrual Phase ($F[1, 36] = 1.20, p = .28$) was not significant for Mechanical Pressure-Pain.
- This suggests pressure-pain did not differ across the mid-follicular and late-luteal phases of the menstrual cycle.

Conclusions

- Results indicated there were no phase-dependent changes in NFR threshold, electrocutaneous pain tolerance, ischemic pain threshold/tolerance, mechanical pressure-pain threshold, and MPQ ratings.
- Electrocutaneous pain threshold was the only pain sensitivity measure shown to vary across the menstrual cycle, with lower thresholds found during the late-luteal phase, relative to the mid-follicular phase.
- This suggests the menstrual cycle may exert little influence on pain sensitivity in healthy women.
- Given that women experience more pain-related symptomatology during the late-luteal phase of their menstrual cycle, and have more chronic pain conditions than men (i.e., fibromyalgia, migraine headache), this research is important in further elucidating the pain/hormone relationship and its impact on pain sensitivity in women.